AT

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/835,759	04/16/2001	Emilio Barbera-Guillem	B-63	5302

21130 7590 05/20/2004

BENESCH, FRIEDLANDER, COPLAN & ARONOFF LLP
ATTN: IP DEPARTMENT DOCKET CLERK
2300 BP TOWER
200 PUBLIC SQUARE
CLEVELAND, OH 44114

EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/835,759	BARBERA-GUILLEM, EMILIO	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) *14-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/16/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 1-68 are pending.

2. Applicant's election with traverse of invention I, claims 1-13 and species (d) "CD-22" and species (h) "monoclonal antibodies" in the Paper filed 2/5/2004 is acknowledged. The traversal is on the grounds that it would not be unduly burdensome to perform a search on claims 1-68 and species A and B together. This is not found persuasive. The restricted Groups have acquired a separate status in the art as a separate subject for inventive effect and require independent searches as set forth in the restriction requirement mailed 11/3/2003. The search for each of the above inventions is not co-extensive particularly with regard to the literature search. A reference, which would anticipate or render obvious one group would not necessarily anticipate or make obvious any of the other groups. Thus, the literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and different patentability issues are involved in the examination of each group. Further, the Examiner notes that rejoinder of claims will be considered once allowable subject matter has been identified in the claims under examination.

For these reasons the restriction requirement is deemed to be proper and is made FINAL.

3. Claims 14-68 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

4. Claims 1-13 are under examination. The claims are being examined to the extent that the affinity ligand is a monoclonal antibody specific for CD22 (LL2).

Specification

5. The disclosure is objected to because of the following informalities:

a. It is requested that applicant update the priority information in the first line of the specification with a benefit claim to Application serial numbers 60/103,350 and 60/117,526. Applicant is reminded that an incorporation-by-reference statement added after the filing date of an application is not permitted because no new matter can be added to an application after its filing date. See United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application", Part VII.

b. On page 21, line 20 of the specification a segmented line is presented and it is unclear what the intended meaning of this segmented line is. Applicant is requested to clarify or remove this line from the specification.

c. The Brief Description of Drawings states that Figure 4 illustrates the effect of various treatments on *in vivo* tumor progression, however, Figure 4 does not identify what the numbered lines represent. It is requested that Applicant update the Brief Description of Drawings for Figure 4 to state what the numbered lines represent.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 6 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 13 are indefinite for reciting "immunotherapeutic composition comprising cobra venom factor". Claims 6 and 13 are depend from parent claims 1 and 9, respectively, which recite "an immunotherapeutic composition for effecting B cell depletion". It is unclear what is contemplated by the recitation that cobra venom factor effects B cell depletion as recited in parent claims 1 and 12, respectively. Does cobra venom factor effect B cell depletion or does cobra venom factor deplete complement or is cobra venom factor an effector of an immunoconjugate that targets and kills cancerous cells?

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. a. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunotherapeutic composition for the treatment of a solid nonlymphoid tumor and for suppressing a TH2 response and inducing a cell mediated immune response comprising a TH1 response in an individual having a TH2/TH1 imbalance mediated by a pro-tumor immune response comprising a composition for affecting B cell depletion, a tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response and an immunomodulator for inducing a TH1 response, does not reasonably provide enablement for a vaccine composition for treating or preventing a solid nonlymphoid tumor and for suppressing a TH2 response and inducing a cell mediated immune response comprising a TH1 response in an individual having a TH2/TH1 imbalance mediated by a pro-tumor immune response comprising a composition for affecting B cell depletion, a tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response and an immunomodulator for inducing a TH1 response nor is there enablement for an immunotherapeutic composition comprising cobra venom factor and a tumor-associated antigen capable of inducing a TH1 response for treating or preventing a solid nonlymphoid tumor and for suppressing a TH2 response and inducing a cell mediated immune response comprising a TH1 response in an individual having a TH2/TH1 imbalance (see claims 6 and 13 and part b below). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to a vaccine composition for suppressing a TH2 response and for inducing a TH1 response in an individual having a TH2/TH1 imbalance and for the treatment and prevention of a solid nonlymphoid tumor in a individual, wherein the vaccine composition comprises a component for effecting B cell depletion and a tumor-associated antigen capable of inducing a TH1 response and the vaccine composition further comprises a component selected from the group consisting of a TH1 inducing immunomodulator, a pharmaceutically acceptable carrier and a combination thereof.

The specification teaches B cell depletion or depletion of shed-antigen specific B cells can inhibit the *in vivo* pro-tumor immune response-mediated progression of solid tumor nonlymphoid tumor (see page 30, example 1). Similarly, results in humans treated with an anti-CD20 monoclonal antibody to deplete B cells resulted in at least two individuals experienced a reduction in the size and number of metastases (see page 31, example 1). The specification also teaches that anti-shed tumor antigen antibody complexes modulate the immune response to a TH2 type response (see example 2 and Figures 1-3). Further, Example 4 teaches that tumor bearing mice, following tumor

resection were subjected to various immunotherapeutic compositions and the treatments indicated that it may be necessary to control (reduce) the TH2 response as part of immunotherapy of an individual against solid nonlymphoid tumor 9see Example 4 and pages 39-40 and Figure 4). The specification does not teach that any particular immunotherapeutic composition was 100% preventative in preventing tumor recurrence and elimination of residual tumorous disease. In fact, Figure 4, line 4 shows that only a majority (e.g., >60%) of mice receiving the treatment of an immunotherapeutic composition, tumor-associated antigen and immunomodulator failed to develop tumor recurrence and also failed to develop detectable metastases (see Figure 4, line 4 and bridging paragraph of pages 39-40).

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual tumorous disease. It is well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Forni et al (Cancer Research, 2000, 60; 2571-2575) disclose tumor cells have the ability to escape immune reactions and tumor masses can suppress immune attack (see page 2571, right column). Mouse models show that elicitation of a significant immune response in patients with advanced tumors is exceedingly difficult, and only a minority of tumor-bearing mice are cured. "As a tumor increases in size, it becomes refractory to immunotherapy" (see page 2571, left column). A similar picture is emerging from Phase I immunotherapy trails where only a few patients with established tumors display objective and in any event temporary responses (see page 2571, right column). Tumor

burden and antigenic drift continue to present serious burdens for successful cancer therapy *in vivo*. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

Donnelly J. (Nature Medicine, 11(9): 1354-1356, Nov. 2003) states "treating cancer with something that looks more like a modern-day vaccine, with a defined antigen and an optimized adjuvant and delivery platform, is still in the future" (see page 1354 lines 13-17). Further, DeGruijl T. D. et al (Nature Medicine, 5(10): 1124-1125, Oct. 1999) state that a variety of anti-tumor vaccine trials have been undertaken and in spite of the large number of these trials, and the plethora of distinct approaches investigated, there has been little evidence of clinical efficacy. DeGruijl also states "precise correlates of clinical effects and immunological responses have been lacking" (see page 1124, left column).

It has been an art-recognized experience that for any novel therapy, the transition from the laboratory to the clinic (animal experiments to bedside) is a quantum leap (Chatterjee et al., Cancer Immunology and Immunotherapy, 38:75-82, 1994). Results obtained under controlled conditions and in inbred animals often differ from the clinical response obtained in patients. This applies in particular to strategies based on immune responses, including strategies drawn to cancer therapy. Bodey et al (Anticancer Research, 20:2665-2676, 2000) acknowledge that general immune activation directed against the target antigens contained within cancer vaccines has been documented in most cases and tumor specific cytotoxic T lymphocytes (CTLs) can

be isolated from the solid tumors, draining lymph nodes, metastatic effusions, and peripheral blood of cancer patients. However, attempts at active specific immunotherapy using cancer vaccines have met with little success in clinical trials (see abstract and page 2668). "Peptide vaccination against tumor antigens can induce powerful systemic CTL responses. However, in the majority of patients, no tumor regression is noted" (see page 2673, left column). Lee et al (Journal of Immunology 163: 6292-6300, 1999) also disclose that a peptide-based vaccine can effectively generate a quantifiable T cell-specific immune response in the peripheral mononuclear cells of cancer patients, though such a response does not associate with a clinically evident regression of metastatic melanoma. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules (see page 2673, right column). "Use of cancer vaccines to stimulate the immune system may be in vain, if the particular tumor associated antigens represented in the vaccine preparation are no longer present on the most advanced subsets of cancer cells" (see pages 2673-2674).

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to induce tumor immunity to prevent tumor recurrence and to eliminate residual tumorous disease by inoculating an individual with a vaccine comprising an immunotherapeutic composition, a tumor-associated antigen and an immunomodulator. The specification does not teach how to extrapolate data obtained from murine animal

models to the development of effective cancer vaccines that result in tumor regression. The specification does not teach how inoculating an individual with immunotherapeutic composition, a tumor-associated antigen and an immunomodulator overcomes the back-and-forth struggle between host and tumor, a process which creates highly resistant, poorly immunogenic, and extremely aggressive clones of tumor cells.

In view of the lack of the predictability of the art to which the invention pertains the lack of established clinical protocols for effective cancer therapies, undue experimentation would be required to practice the claimed vaccine with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed vaccine and absent working examples providing evidence which is reasonably predictive that the claimed vaccine is effective for vaccinating individuals against cancer, commensurate in scope with the claimed invention.

b. Claims 6 and 13 are also drawn to an immunotherapeutic composition comprising cobra venom factor and a tumor-associated antigen capable of inducing a TH1 response for treating or preventing a solid nonlymphoid tumor and for suppressing a TH2 response and inducing a cell mediated immune response comprising a TH1 response in an individual having a TH2/TH1 imbalance.

The specification teaches B cell depletion or depletion of shed-antigen specific B cells can inhibit the *in vivo* pro-tumor immune response-mediated progression of solid tumor nonlymphoid tumor (see page 30, example 1). Similarly, results in humans treated with an anti-CD20 monoclonal antibody to deplete B cells resulted in at least two

individuals experienced a reduction in the size and number of metastases (see page 31, example 1). The specification also teaches that anti-shed tumor antigen-antibody complexes modulate the immune response to a TH2 type response (see example 2 and Figures 1-3). Further, Example 4 teaches that tumor bearing mice, following tumor resection were subjected to various immunotherapeutic compositions and the treatments indicated that it may be necessary to control (reduce) the TH2 response as part of immunotherapy of an individual against solid nonlymphoid tumor (see Example 4 and pages 39-40 and Figure 4). The specification does not teach an immunotherapeutic composition comprising cobra venom factor and a tumor-associated antigen that suppresses a TH2 response and induces a TH1 response nor does the specification teach an immunotherapeutic composition comprising cobra venom factor and a tumor-associated antigen for treating a solid nonlymphoid tumor. Further, the specification provides insufficient guidance with respect to optimized dosages and regimens for the administration of an immunotherapeutic composition comprising cobra venom factor and a tumor-associated antigen, wherein said administration suppresses a TH2 response and induces a TH1 response in an individual and is therapeutically effective for treating solid nonlymphoid tumors. The specification provides no working examples to guide the skilled artisan.

Morgan et al (Molecular Immunology 40:159-170, 2003) teach that cobra venom factor is known to bind mammalian fB in plasma and, after cleavage of fB by fD, produces a C3 convertase that is stable and resistant to the fluid phase regulators (see page 159, right column). Morgan et al teach that cobra venom factor consumes all

plasma C3, thereby obliterating functional complement in an animal for up to a week (see pages 159-160). However, beyond this time, cobra venom factor becomes ineffective because of a strong immune response with generation of neutralizing antibodies in the recipient according to Morgan et al (see page 160, left column). The instant specification does not take into account these neutralizing antibodies nor does it address how cobra venom factor is "effective for B cell depletion" and the prior art does not teach cobra venom factor as "effective for B cell depletion". Morgan et al state "most practicioners agree that cobra venom factor has no direct role in human disease. The strong antibody response ensures that any benefit would be short lived and the uncontrolled complement activation that accompanies cobra venom factor decomplementation could potentially precipitate iatrogenic shock syndromes, as observed in some animal models." (see pages 160-161). Further, according to Morgan et al it is becoming impossible to source cobra venom factor and hopefully, recombinant cobra venom factor may become available in the near future (see page 161, left column).

No direction or guidance is provided to assist one skilled in the art in the selection of all such possible immunotherapeutic compositions comprising cobra venom factor and a tumor-associated antigen for suppressing a TH2 response and inducing a TH1 response in an individual, nor is there evidence that such a composition would be therapeutically effective for treating a solid nonlymphoid tumor. In view of the discussion above and the teachings of Morgan et al and the lack of guidance and working examples in the specification, it appears that undue experimentation would be

required of the skilled artisan to practice the claimed immunotherapeutic composition as an effective treatment for solid nonlymphoid tumor and for suppressing a TH2 response and inducing a TH1 response.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 2, and 7-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Noguchi et al (Proc. Natl. Acad. Sci. USA, 92:2219-2223, 1995) as evidenced by the specification (see page 11) and as evidenced by Trinchieri G. (Immunology Today, 14(7):335-338, 1993).

The claims are interpreted as being drawn to an immunotherapeutic composition comprising a component for effecting B cell depletion, a tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response, wherein the immunotherapeutic composition further comprises a component selected from the group consisting of an immunomodulator for inducing a cell mediated immune response comprising a TH1 response, a pharmaceutically acceptable carrier and a combination thereof. For this rejection the intended use as an immunotherapeutic

composition for suppressing a TH2 response and for inducing a cell mediated immune response comprising a TH1 response in an individual having a TH2/TH1 imbalance mediated by a disease process comprising a pro-tumor immune response and solid nonlymphoid tumor is given no patentable weight.

Noguchi et al teach a composition comprising a nonamer p53 peptide (i.e., tumor –associated antigen) in QS-21 adjuvant, and IL-12, which is interpreted as an effector of B cell depletion. As evidenced from the specification at page 11, QS-21 induces a TH1 response, which is known by the skilled artisan. Therefore, QS-21 is interpreted as an immunomodulator that induces a TH1 response. Further, it is inherent that IL-12 induces a TH1 or cell-mediated response and inhibits a TH2 or humoral (i.e. antibody or B cell response) response as evidenced by Trinchieri G. Trinchieri G. teaches that IL-12 induces a TH1 response and inhibits a TH2 type or humoral response. Therefore, IL-12 is interpreted as an effector of B cell depletion as well as an immunomodulator that induces a TH1 response (see Figures 1 and 2). Thus, Noguchi et al anticipate the claims as evidenced by Trinchieri G.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claims 1-5 and 7-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Apostolopoulos et al (Vaccine, 14(9):930-938, 1996) in view of Tachibana et al (Tokai Journal of Experimental Clinical Medicine 8(5-6):455-463, 1983) and Trinchieri G. (Immunology Today, 14(7):335-338, 1993) and Parkhouse et al (Current Topics in Microbiology and Immunology, 182:331-335) and Wang P. Y-C. (U.S. Patent 5,939,380, filed 1991).

The claims are interpreted as being drawn to an immunotherapeutic composition for suppressing a TH2 response and for inducing a cell mediated immune response (i.e., TH1) in an individual having a TH2/TH1 imbalance mediated by a pro-tumor immune response and solid nonlymphoid tumor comprising a component for effecting B cell depletion, a tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response, wherein the immunotherapeutic composition further comprises a component selected from the group consisting of an immunomodulator for inducing a cell mediated immune response comprising a TH1 response, a pharmaceutically acceptable carrier and a combination thereof. The immunotherapeutic composition further comprises an anti-B cell agent and a CD22

monoclonal antibody. The claims are also drawn to the above immunotherapeutic composition for treating a solid nonlymphoid tumor in an individual.

Apostolopoulos et al teach that induction of a humoral immune response (i.e., TH1 response) gives poor tumor protection accompanied by little cellular immunity (i.e., TH2 response), however, when a cellular immune response is induced, this results in significant tumor protection, cytotoxic T lymphocytes and little antibody production (i.e., TH1 or humoral immune response) (see abstract and page 930, right column). Apostolopoulos et al state "However, in immunotherapy studies mice immunized with either natural mucin (HMFG) or a 20mer synthetic peptide from the VTNR repeat or a MUC1 fusion protein (FP), and challenged with MUC1^{+}3T3 cells, had poor tumor protection; significant antibody titers were produced, a detectable CD4^{+} DTH, but no CTL were found." (see page 930, right column). Apostolopoulos et al do not specifically teach an immunotherapeutic composition comprising a component for effecting B cell depletion, a tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response, further comprising a component selected from the group consisting of an immunomodulator for inducing a cell mediated immune response comprising a TH1 response, a pharmaceutically acceptable carrier and a combination thereof and an anti B cell agent and a CD22 monoclonal antibody. These deficiencies are made up for in the teachings of Tachibana et al and Trinchieri G. and Parkhouse et al and Wang P. Y-C.

Tachibana et al teach that enhancement of tumor growth was caused by acceleration of the humoral response (i.e., TH2 response; TH2/TH1 imbalance) existing

in the tumor bearing state (see page 461 and abstract). Specifically, Tachibana et al teach that in mice with enhanced tumors, the level of immune complexes and antitumor antibodies in sera was more markedly elevated than in sera of untreated tumor-bearers (see abstract). Tachibana et al teach that combined treatment with cyclophosphamide (an immunosuppressant to depress humoral response and/or regulatory cells; see page 456) plus hybrid cells showed no antibody elevation and immune complex production, but generation of potent cytotoxic T cells was comparable to that of immunized hosts and was followed by curative antitumor effect (see page 461).

Trinchieri G. teaches the immunomodulator, IL-12, which induces a cell mediated or TH1 response and negatively regulates or inhibits a TH2 type response (see Figures 1-2).

Parkhouse et al teach that normal B cells bear surface CD22 and an anti-CD22 antibody-ricin conjugate effectively depletes normal B cells (see Figure 3).

Wang P. Y-C. teach solid phase implants for the delivery of biological macromolecules (see entire document).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an immunotherapeutic composition for suppressing a TH2 response and inducing a TH1 response comprising a component for effecting B cell depletion, a tumor-associated antigen capable of inducing a TH1 response, and a component selected from an immunomodulator for inducing a TH1 response, a pharmaceutical composition or a combination thereof for therapeutic benefit of a solid nonlymphoid tumor.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced an immunotherapeutic composition for suppressing a TH2 response and inducing a TH1 response comprising a component for effecting B cell depletion, a tumor-associated antigen capable of inducing a TH1 response, and a component selected from an immunomodulator for inducing a TH1 response, a pharmaceutical composition or a combination thereof for therapeutic benefit of a solid nonlymphoid tumor in view of Apostolopoulos et al and Tachibana et al and Trinchieri G and Parkhouse et al and Wang P. Y-C because Apostolopoulos et al teach that induction of a humoral immune response (i.e., TH2 response) gives poor tumor protection accompanied by little cellular immunity (i.e., TH1 response), however, when a cellular immune response (TH1) is induced, this results in significant tumor protection, cytotoxic T lymphocytes and little antibody production and Tachibana et al teach that enhancement of tumor growth was caused by acceleration of the humoral response (i.e., TH2 response; TH2/TH1 imbalance) existing in the tumor bearing state. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced an immunotherapeutic composition for suppressing a TH2 response and inducing a TH1 response comprising a component for effecting B cell depletion, a tumor-associated antigen capable of inducing a TH1 response, and a component selected from an immunomodulator for inducing a TH1 response, a pharmaceutical composition or a combination thereof for therapeutic benefit of a solid nonlymphoid tumor in view of Apostolopoulos et al and Tachibana et al and Trinchieri G and Parkhouse et al and Wang P. Y-C because

Trinchieri G. teaches an immunomodulator, IL-12, which induces a cell mediated or TH1 response and negatively regulates or inhibits a TH2 type response. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced an immunotherapeutic composition for suppressing a TH2 response and inducing a TH1 response comprising a component for effecting B cell depletion, a tumor-associated antigen capable of inducing a TH1 response, and a component selected from an immunomodulator for inducing a TH1 response, a pharmaceutical composition or a combination thereof for therapeutic benefit of a solid nonlymphoid tumor in view of Apostolopoulos et al and Tachibana et al and Trinchieri G and Parkhouse et al and Wang P. Y-C because Parkhouse et al teach that normal B cells bear surface CD22 and an anti-CD22 antibody-ricin conjugate effectively depletes normal B cells and Wang P. Y-C. teach solid phase implants for the delivery of biological macromolecules. Therefore, it would have been obvious to one skilled in the relevant art to produce an immunotherapetic composition comprising the TH1 immunomodulator, IL-12 as taught by Triunchieri G and an anti-CD22 antibody-ricin conjugate (i.e., anti-B cell agent) for B cell depletion as taught by Parkhouse et al because Apostolopoulos et al teach that induction of a humoral immune response (i.e., TH2 response) gives poor tumor protection, whereas a cellular immune response (i.e., TH1 response) results in significant tumor protection, and Apostolopoulos et al and Tachibana et al high antibody titers (i.e., humoral immune response) correlate with poor tumor protection and it would have been obvious to the skilled artisan to use a solid phase implant to facilitate the administration of the immunotherapeutic composition.

Thus, it would have been obvious to one skilled in the art to produce an immunotherapeutic composition for suppressing a TH2 response and inducing a TH1 response comprising a component for effecting B cell depletion, a tumor-associated antigen capable of inducing a TH1 response, and a component selected from an immunomodulator for inducing a TH1 response, a pharmaceutical composition or a combination thereof for therapeutic benefit of a solid nonlymphoid tumor in view of Apostolopoulos et al and Tachibana et al Trinchieri G and Parkhouse et al and Wang P. Y-C.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at (571) 272-0827 from 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841.

Official papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published

in the Official Gazette, 1096 OG 30 (November 15, 1989). The official fax number for Group 1600 where this application or proceeding is assigned is (703) 872-9306.

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER